REMARKS

Status of the Claims

Claims 1-39 were pending prior to entry of the present amendment.

Claims 1-39, currently under examination, stand rejected.

Claims 31-39 are cancelled herein without waiver of Applicants' right to pursue the cancelled subject matter in one or more continuation applications.

Claims 1-4, 6-8, 16, 17, and 25 are amended herein. No new matter is introduced.

Interview Summary

Applicants wish to thank Examiner Amy H. Bowman for the courtesy extended to Applicants' representatives Jonathan Ball and Deborah Drazen during the telephonic interview of February 19, 2008. During the interview, all of the outstanding rejections from the Office Action mailed on December 7, 2007 were discussed.

With respect to the enablement rejection, it was discussed that the rejections would be overcome by amending the claims such that each pending claim would recite topical administration of the siRNA oligomers, and that the method would be directed to reducing melanin production, rather to treating "unwanted pigmentation associated with production of melanin." It was also discussed that Applicants would amend the claims to provide more structural specificity concerning the siRNA oligomers in order to address the written description rejection. Examiner Bowman agreed that the prior art rejections over Bennett (US Patent Pub. 2004/0215006) would merit reconsideration in view of the amendments discussed.

Amendment to the Specification

The specification is amended herein consistent with the claim amendments of October 9, 2007 which eliminated two duplicate sequences inadvertently included in the claims. The amended specification reflects the appropriate sequences.

Support for Claim Amendments

Claim 1 is amended herein to recite a method of "inhibiting the production of melanin in a human" comprising topically administering to the skin of said human, "a composition

comprising a double-stranded small interfering RNA (siRNA) oligomer having a sequence complementary to a sequence found in mouse and native human tyrosinase mRNA; said siRNA oligomer comprising two strands, each of said strands comprising between 15 and 21 nucleotides, including two thymidine nucleotide 3' overhangs," the composition being applied in an amount effective to reduce production of melanin.

The amended claim language finds support throughout the application as filed, and in particular in the following paragraphs: [0007] ("the present invention relates to compositions and methods comprising double-stranded small interfering RNA oligomers (siRNA) to inhibit the production of tyrosinase in a subject"); [0007] ("The siRNA inhibit production of the tyrosinase protein by binding to a specific complement sequence found in the tyrosinase mRNA"); [0017] ("The first three siRNA shown above are homologous to sequences found in both human and mouse forms of tyrosinase"); [0029] ("The invention relates to the use of siRNA oligomers that . . . have a sequence complementary to native human tyrosinase mRNA"); [0040] ("double-stranded siRNA structures can then be directly applied to the skin"); and [0042] ("the siRNA can be stabilized by including thymidine or uridine nucleotide 3' overhangs"), for example.

With respect to the range of "between 15 and 21 nucleotides" recited in amended claim 1, the instant specification discloses the range "between 15 and 30," as well as a preferred embodiment of 21 in paragraph [0029][1], and exemplifies double stranded siRNA oligomers wherein each strand has 21 nucleotides, including two thymidine 3' overhangs at paragraphs [0030]–[0037]. Applicants submit that this provides legally sufficient support for the range "between 15 and 21 nucleotides" because having been in possession of the broad range ("between 15 and 30") and an embodiment within that broad range ("21"), one skilled in the art would understand that Applicants were in possession of the sub-range defined thereby (e.g., "between 15 and 21"). See In re Wertheim, 541 F.2d 275, 191 USPQ 90 (CCPA 1976) (holding

[1] Paragraph [0029] erroneously refers to the number of "oligonucleotides" that are within the siRNA oligomers, rather than the number of "nucleotides." Applicants submit that this error would be instantly apparent to the skilled artisan and would be regarded as nothing more than a typographical error. Based on the knowledge in the art and the disclosure itself, one skilled in the art would understand that the numerical ranges refer to the number of nucleotides in each strand. For example, the last sentence of paragraph [0029] states that "the invention relates to an siRNA oligomer that is 21 *oligonucleotides* in length and has the following sequence . . ." The referenced sequences are those listed in paragraphs [0030]–[0037] which quite clearly comprise 21 *nucleotides* (rather than oligonucleotides).

that a claimed range of "between 35% and 60%" was supported by the disclosure of the range "25 to 60%" and a specific example at 36%).

Accordingly, Applicants submit that no new matter is introduced by the amendments and respectfully submit entry thereof.

Claim Rejections

35 U.S.C. §112, first paragraph: enablement

The Examiner has maintained the rejection of claims 1-39 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth in the Office Actions dated March 30, 2007, and July 10, 2007. Briefly, the Examiner contends that the instant application lacks enablement because as a technology, siRNA delivery is unpredictable, and because the successes of the art of record do not support treating any hyperpigmentation or any unwanted pigmentation associated with production of melanin. Applicants respectfully disagree for the reasons already of record, and in particular because topical siRNA delivery has generally proven to be successful and because it is well known that tyrosinase is associated with hyperpigmentation and with other unwanted pigmentation. Applicants nonetheless have amended the claims in order to advance prosecution. The claims as amended are directed to the inhibition of melanin and no longer recite treatment any "other unwanted pigmentation associated with the production of melanin." Applicants respectfully submit that the rejection has been overcome.

35 U.S.C. §112, first paragraph: written description

The Examiner has rejected claims 1-3 and 5-31 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner states that Applicants have "not closed mouse or human tyrosinase to any single sequence in the claims." Applicants respectfully traverse the rejection. The Examiner points out that in the response filed October 9, 2007, Applicants cited GenBank no. gi:340039 for human tyrosinase, while GenBank accession no. M27160.1 refers to human tyrosinase with a different number of base pairs. Applicants regretfully acknowledge that in the prior submission, the incorrect GenBank no. was cited. The entry erroneously cited by Applicants relates to mutant tyrosinase which was derived from a patient with tyrosinase-negative oculocutaneous albinism. The entry cited by the Examiner,

GenBank accession no. M27160.1 which was cited in the Bennett application, is the correct GenBank entry for normal human tyrosinase. Applicants thank the Examiner for calling this to Applicants' attention, and submit that the correct sequences for the native human and mouse tyrosinase sequences are properly described in Bennett and readily ascertainable to one skilled in the art. Applicants' amended claims now recite "native human tyrosinase," to further define the mRNA which is the subject of the claims. In view of at least the foregoing, Applicants respectfully request withdrawal of the rejection.

35 U.S.C. §102(e) and 35 U.S.C. §103(a)

The Examiner has rejected claims 1-3, 5-9, 14-25, and 31 under 35 U.S.C. §102(e) as being anticipated by Bennett et al. (US Patent Pub. 2004/0215006). The Examiner also maintains the rejection of claims 1-3 and 5-31 under 35 U.S.C. §103(a) as unpatentable over Bennett et al. in view of Mahashabde et al. (US 6,436,378) and Perricone (US 2002/0141956). Applicants respectfully traverse the rejection.

The claims as amended require a siRNA molecule that comprises a complementary sequence to mRNA for both mouse and native human tyrosinase. The claimed siRNA comprise two strands, each having 15-21 nucleotides, including two thymidine nucleotide 3' overhangs. The Examiner has noted that SEQ ID NO: 27 from Table 1 of Bennett lists a sequence which is shared between mouse and human DNA (and consequently, the corresponding mRNA). Applicants note that SEQ ID NO: 27 comprises 20 nucleotides. If one were to include the two thymidine nucleotide 3' overhangs recited in claim 1 on SEQ ID NO: 27, each strand would comprise 22 nucleotides, rather than the claimed 15-21 nucleotides. Accordingly, an siRNA molecule based on SEQ ID NO: 27 would not anticipate the present claims. Moreover, Applicants submit that there would be no motivation to target 15-21 consecutive nucleotides of an RNA region commonly shared by mouse and human based on the disclosure of Bennett because Bennett separately considers mouse mRNA and human mRNA, and apparently only coincidentally lists a sequence in common between the two; i.e., SEQ ID NO: 27, although notably Bennett doesn't disclose that this sequence is common between mouse and human mRNA, nor does Bennett teach or suggest any advantage to targeting a sequence in common between mouse and human mRNA. For at least these reasons, Applicants respectfully submit that the narrow genus of siRNA molecules comprising 15-21 nucleotides in each strand

(including two thymidine 3' overhangs), which are complementary to regions of tyrosinase shared between human and mouse fully distinguishes over Bennett.

Regarding Mahashabde and Perricone, neither of these references either teaches or suggests the use of siRNA oligomers for inhibiting the production of tyrosinase as recited in the instant claims and that therefore do not rectify the deficiencies of Bennett. Therefore, Applicants submit that the rejections under 35 U.S.C. §102(e) and 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

Based on the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of the rejection of claims and allowance of this application.

Respectfully submitted,

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